

# Impact and Perceptions of Mandatory Tumor Biopsies for Correlative Studies in Clinical Trials of Novel Anticancer Agents

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## ABSTRACT

### Purpose

To assess the impact and perceptions of patients, physicians, and institutional review board members (IRBs) on the issue of mandatory serial tumor biopsies to acquire tissues for correlative studies.

### Patients and Methods

Complementary, self-administered questionnaires were circulated to trial patients who had previously undergone serial research-related biopsies (TPs), clinic patients who had prior diagnostic but not research-related biopsies (CPs), academic medical oncologists in Canada (MOs), and IRBs at the affiliated academic centers.

### Results

Ten (72%) of 14 TPs, 265 (82%) of 325 CPs, 137 (66%) of 209 MOs, and 142 (49%) of 291 IRBs responded. A 5% to 10% risk of a major biopsy complication was acceptable to 22% of CPs but only to 1% of MOs or IRBs. Anxiety was reported by 30% of TPs and 45% of CPs before their biopsies. More than 82% of MOs or IRBs believed the average patient would have at least borderline anxiety before their biopsy. Among the patients, 84% would authorize their samples for additional unrelated research and 75% would agree to genetic testing. Nearly all MOs and 86% of IRBs considered it ethical to request for additional unrelated research testing. With respect to genetic testing, 82% of MOs and 72% of IRBs would request it.

### Conclusion

Although nearly all MOs and IRBs see the value in the biopsy, their threshold for acceptable risk is lower and they anticipate more associated anxiety than patients. Most patients recalled a tendency to tolerate their biopsies well with an average associated anxiety, and would allow their specimens to be tested for research purposes.

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## INTRODUCTION

Cancer evolution results from aberrations in genetic and epigenetic processes, which are essential for cellular function, differentiation, survival, and proliferation. Molecularly targeted agents offer attractive therapeutic options by restoring normal control to oncogenic processes. Although cytotoxic chemotherapy drugs typically produce myelosuppression, the toxicity profiles of molecularly targeted agents are less predictable. The standard phase I paradigm of dose escalation based on toxicity may not apply to the development of these agents; biologic end points may be more relevant for dose finding.<sup>1,2</sup> Early-phase studies of molecularly targeted agents often incorporate serial tumor biopsies to measure the agents' biologic effects on target molecules or cellular pathways within the tumor.<sup>3,4</sup>

A biomarker is a characteristic that is measured objectively and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.<sup>5</sup> Several biomarkers have been identified that predict for response to treatment such as HER2<sup>6</sup> and the Philadelphia chromosome.<sup>7</sup> Correlative biomarkers can validate an association between clinical outcome and the targeted agent's effect on the putative molecule or cellular pathway.<sup>8,9</sup> The procurement of tumor tissues via serial biopsies, along with plasma drug levels and surrogate markers in nontumor tissues, may be correlated with clinical outcome to provide insight into the actual modulation of the target. These end points are often incorporated into the trial design of new anticancer agents and may be relevant in their development.<sup>2,5,10-13</sup>

A 10-year review, performed by the Case Western group of seven phase I and II clinical trials in

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which paired tumor biopsies were mandatory, a study of gefitinib in metastatic colorectal cancer patients, and a phase II study of gefitinib in patients with advanced breast cancer all confirm that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early-phase clinical trials.<sup>14-16</sup> However, little is known or published on patients', physicians', or institutional review board members' acceptance of and perceptions associated with mandatory, sequential, research-related tumor biopsies. We conducted a self-administered survey to assess the perceptions associated with mandatory biopsies; specifically, the impact on trial enrollment, the importance of these biopsies for clinical research, the acceptable risks attributed to the biopsies, the emotional impact that these biopsies may have on the patients, and the role of additional unrelated testing on the acquired samples. Our study did not seek to evaluate the scientific value of the research-related biopsies, which remains a controversial topic outside the scope of this survey.

## PATIENTS AND METHODS

Four complementary, self-administered questionnaires (Appendix Fig A1, online only) were circulated to trial patients who previously had undergone serial research-related tumor biopsies (TPs), clinic patients who had prior diagnostic but not research-related biopsies (CPs), academic medical oncologists in Canada (MOs), and IRB members at the affiliated academic centers (IRBs). All questionnaires contained a cover letter explaining the study, invited voluntary participation, and informed participants that they may omit questions. Participation was anonymous, confidential, and without incentive.

Questionnaires inquired about demographics, perceptions on trials mandating tumor biopsies, acceptable risks attributable to tumor biopsies, and perceptions on the ethics of additional unrelated testing on the tumor samples. Patient questionnaires incorporated the anxiety components of the Hospital Anxiety and Depression Scale (HADS)<sup>17</sup> to assess their recall of their anxiety level before and after the biopsy procedure. MOs and IRBs were questioned on the presumed degree of anxiety caused by the biopsy in the average patient.

### Patient Questionnaires

TPs identified through the Princess Margaret Hospital (Toronto, Ontario, Canada) Drug Development Program database, with the approval of their responsible physicians, were mailed a questionnaire in October 2004. A second mailing occurred 2 weeks later. This questionnaire consisted of 39 multiple-choice questions and one question requesting the patient's age. CPs' questionnaires were distributed in the ambulatory medical oncology cancer clinics at the Princess Margaret Hospital, a comprehensive Canadian cancer center hospital, for a 2-week period in November 2004. This questionnaire differed by omitting the two questions that focused on the clinical trial in which the TPs had participated.

### Questionnaires for MOs and IRBs

MOs affiliated with 13 Canadian universities were chosen for this study. Lists were obtained from an Internet search of the medical oncology department at each university. The questionnaires were mailed in October 2004 and a second mailing occurred 2 weeks later. The questionnaire consisted of 29 multiple-choice questions and two questions requesting the respondent's age and year of certification, respectively. IRB administrators from the associated hospitals were contacted and nine agreed to distribute questionnaires to each of their members; one IRB required local ethics approval, which was obtained; two IRBs refused participation without reason; and one center was excluded because a French questionnaire was not available for their members. IRB questionnaires were distributed between October and December 2004. A single mailing was used, given that a third party was required for distribution. These questionnaires omitted the 10 questions that dealt with the MOs' clinical trial experience and patient interaction.

## Statistical and Study Analysis

Summary statistics were used to describe the demographics and survey responses for each cohort separately. Data were compared between CPs who completed the survey and those who did not using  $\chi^2$  tests for binary variables and a Wilcoxon rank sum test for age. Change in anxiety level was tested using a McNemar test. The Kruskal-Wallis test was used to investigate for differences in risk tolerance. Selected demographic characteristics were investigated for associations with selected attitudes using  $\chi^2$  tests. Dichotomization of variables occurred throughout the analysis where necessary for statistical power considerations. All tests were two sided and a *P* value of .05 or less was considered statistically significant.

Questionnaires were pilot tested by six oncologists, two nurses, and seven patients to ensure validity, clarity, and ease of administration. One member (M.A.) entered the results independently into a database, which was checked manually for accuracy by random selection of 53 questionnaires. Ten questions from each of the random questionnaires were verified between the source document and the database, with a resulting error rate of 0.01%.

The IRB at the University Health Network approved the questionnaires. To protect confidentiality and anonymity, no signed consent form was required to participate in this survey for any party involved.

## RESULTS

### Questionnaires From TPs and CPs

Fourteen TPs were alive at the time of the questionnaire mailing. Ten questionnaires (71%) were returned, all of which were complete. Questionnaires were circulated to 325 CPs, of which 265 questionnaires (82%) were returned and 231 (87%) of 265 were assessable. Of the 34 nonassessable questionnaires, all contained answers to questions assessing demographics, but none had answers to questions beyond the demographics section. In comparing evaluable and non-assessable questionnaires, CPs who completed the questionnaires, beyond the demographics section, were more likely to report having had prior therapy for their malignancy. Patient demographics and clinical characteristics are summarized in Table 1.

Patients' biopsy experience is summarized in Table 2. All TPs and 86% of CPs reported having a previous biopsy. Most TPs and 49% of CPs believed they were adequately informed about biopsy-related adverse effects and risks, and few reported a related adverse effect. The need for research-related biopsies as part of a clinical trial would deter 36% of CPs from enrolling. Although it was explained clearly in the cover letter and questionnaire that the biopsy specimens would be for research purposes only, about half of patients still believed that having these biopsies might impact their care and health.

### Questionnaires From MOs and IRBs

After two mailings, 137 of 209 (66%) mailed MO questionnaires were returned. Two had been returned because the physicians had moved and one was returned from a physician who did not practice medical oncology. As such, 134 MO questionnaires were used for analysis. IRB administrators were sent a total of 291 questionnaires for distribution: 142 (49%) were returned, 123 were assessable, and 19 were blank. Demographics of the MO and IRB respondents are listed in Table 3. All results are based on responses self-reported by MOs and IRBs.

Of those who responded, 55% and 96% of MOs enroll patients and 76% and 70% refer patients into phase I and II clinical trials, respectively. For trials mandating research biopsies, 48% of MOs have directly enrolled and 45% have referred patients into these trials. In consenting patients for biopsies, 73% of MOs believed patients

**Table 1.** Characteristics of TPs and CPs

Characteristic	TPs	CPs With Complete Survey	CPs With Incomplete Survey	P*
Total No. of patients	10	231	34	
Age, years				
Median	55	60	61	
Range	37-75	22-84	38-84	.33
Sex, %				
Male	60	39	47	.35
Female	40	60	50	
Missing data	0	1	3	
Race/ethnicity, %				
White	100	80	76	.81
Nonwhite	0	17	21	
Missing data	0	3	3	
English speaking, %				
Yes	80	69	50	.070
No	20	31	50	
Education, %				
≤ High school	70	39	51	.080
> High school	30	49	39	
Missing data	0	2	10	
Disease site, %				
Breast	0	41	29	Not done
GI	60	25	26	
Genitourinary	0	15	9	
Head and neck	10	10	9	
Other	40	8	9	
Missing data	0	1	18	
Prior treatment, %				
Yes	100	89	68	.006
No	0	10	26	
Missing data	0	1	6	
Self-report presence of metastatic disease, %				
Yes	80	41	29	.24
No	20	48	50	
Missing data	0	11	21	

Abbreviations: TPs, trial patients; CPs, clinic patients.

\*Calculated from comparison of CPs who completed survey with those who did not complete survey, excluding patients with no answer.

**Table 2.** Information on Biopsies: Patient Questionnaires

Question	TPs (%)	CPs (%)
Reported having had a previous biopsy		
Yes	100	86
No	0	13
Missing data	0	1
Site of biopsy (of those with previous biopsy)		
Abdomen	80	24
Breast	0	40
Head and neck	20	12
Other	0	23
Cannot remember	0	2
Missing data	0	16
Do you feel that the adverse effects and risks of the tumor biopsy were adequately explained to you before it was done?		
Yes	90	49
No	10	23
Cannot remember	0	13
Missing data	0	14
Did you have a biopsy adverse effect?		
Yes	30	29
No	70	52
Cannot remember	0	3
Missing data	0	16
If yes, what adverse effect did you have? (of those with adverse effect)		
Bleeding	0	29
Infection	0	9
Pain	100	79
Other	0	6
Would the need for research-related biopsies deter you from enrolling into a clinical trial?		
Yes	N/A	36
No		48
Missing data		16
What impact will the research-related biopsies have on your health and care?		
Will impact	20	42
May or may not impact	50	15
No impact	30	30
Missing data	0	13

Abbreviations: TPs, trial patients; CPs, clinic patients; N/A, not applicable.

received adequate explanation of the procedure and 63% believed that patients received adequate explanation of the adverse effects and risks.

The views of MOs and IRBs about the role of the serial biopsies in clinical trials are outlined in Table 4. Most believed the requirement is ethical but ideally an option should be given, and presumed that most patients would prefer not to have the biopsy. The mandatory biopsies are believed to influence trial enrollment negatively by 21% of MOs and 52% of IRBs. The majority of MOs believed that the incorporation of mandatory biopsies would cause a delay in treatment.

### **Anxiety Reported by Patients and Presumed by MOs and IRBs**

Table 5 summarizes the anxiety levels associated with tumor biopsies as recalled by TPs and CPs, using items based on the anxiety components of the HADS. MOs and IRBs were asked about the presumed degree of anxiety caused by the biopsy in the average patient. The largest proportion of patients reported normal anxiety levels prebiopsy, whereas the majority of MOs and IRBs presumed that

patients would have borderline anxiety prebiopsy. Although the levels of anxiety experienced by patients and presumed by MOs and IRBs were both reduced postbiopsy, the discrepancies in the responses between the patient and nonpatient groups persisted.

### **Acceptable Risks of Research-Related Biopsies**

Acceptable risk levels attributed to research-related biopsies were assessed. Categories were specified as follows: a major complication requiring surgical intervention, pain requiring analgesia, infection requiring antibiotics, and bleeding requiring intervention. Results show similar views on the acceptable risks of pain, which is the most acceptable risk category, but varied attitudes with respect to the acceptable risks of a major complication, infection, and bleeding (Fig 1). Clearly, patients would accept higher risks of a major complication,

**Table 3.** Characteristics of MOs and IRBs

Characteristic	MOs	IRBs
No.	134	123
Age, years		
Median	44	49
Range	29-70	27-77
Sex, %		
Male	58	56
Female	42	42
Missing data	0	2
Job description, %		
Ethicist/lawyer/statistician	0	18
Lay person	0	17
Pharmacist/nurse	0	14
Oncologist	93	15
Physician (nononcologist)	7*	24
Other	0	11
Year certified		
Median	1994	N/A
Range	1962-2004	N/A

Abbreviations: MOs, medical oncologists; IRBs, institutional review board members; N/A, not applicable.  
 \*All nononcologist MOs classified themselves as hematologists.

infection, and bleeding, when compared with MOs or IRBs. MOs accept higher degrees of risk from these biopsies when compared with IRBs in all risk categories.

### Additional Unrelated Testing on Tumor Samples

Respondents' views on additional testing of the research biopsy specimens are summarized in Table 6. No TPs and 4% of CPs would have their tissues destroyed. Although 90% and 75% would allow genetic testing, 100% and 82% of TPs and CPs, respectively, want results if they were informative about their health. MOs indicated unanimously that requests for authorization to conduct additional unrelated testing on the samples are ethical, whereas 10% of IRBs view these requests as unethical. For the collected tissues, 10% of MOs and 31% of IRBs believe they should be destroyed. Genetic testing would be requested by most MOs and IRBs, though fewer would inform patients of the results.

### Univariate Analysis

Selected univariate analyses were performed to assess whether demographic features predict for different attitudes in CPs, MOs, or IRBs. For CPs, English-speaking patients are more willing to enroll onto clinical trials with mandatory tumor biopsies, those with a higher degree of education are more likely to allow additional research and genetic testing on their tumor specimens, and men report less anxiety before and after their biopsies. MOs who are older than the median age are more inclined to request for additional testing on the tissue specimens (85% v 68%;  $P = .034$ ). IRBs who have direct patient contact are more likely to request for genetic testing on the patients' tumor samples (86% v 68%;  $P = .029$ ).

## DISCUSSION

Patients, MOs, and IRBs clearly have different views regarding the issue of mandatory research-related tumor biopsies. The procurement

**Table 4.** Information on Biopsies: MOs and IRBs

Question	MOs (%)	IRBs (%)
Are research biopsies worthwhile?		
Yes	93	83
No	4	4
Missing data	3	13
Is it ethical to require a research biopsy in order to participate in the trial?		
Yes	72	64
No	22	25
Missing data	6	11
Should patients be given an option to have the research biopsies?		
Yes	66	67
No	30	24
Missing data	4	9
Does this requirement negatively impact enrollment?		
Yes	21	52
No	74	36
Missing data	5	12
Would three research biopsies be too many?		
Yes	47	41
No	48	45
Missing data	5	14
What best describes patients' attitudes toward these trials with mandatory research biopsies?		
Do not mind having the biopsies	25	24
Do not want to have the biopsies	65	56
Missing data	10	20
Do research biopsy requirements cause a delay in treatment?		
Yes	67	N/A
No	31	
Missing data	2	

Abbreviations: MOs, medical oncologists; IRBs, institutional review board members; N/A, not applicable.

of research biopsy specimens was believed to be worthwhile by the vast majority of MOs and IRBs. This finding is substantiated by the observations that many early-phase clinical trials of molecularly targeted agents have incorporated research biopsies into their trial designs. The results from tumor biopsies have been shown in some cases to assist in phase II dose recommendations and to allow comparison of the effects observed in tumor tissues and surrogate markers. For instance, a phase I trial of O<sup>6</sup>-benzylguanine in patients undergoing surgery for malignant gliomas recommended drug dosing based on protein levels measured in the tumors removed at surgery.<sup>18</sup> A phase II study of gefitinib in patients with advanced breast cancer revealed inhibition of phosphorylation of epidermal growth factor receptor and mitogen-activated protein kinase in both skin and tumor biopsies.<sup>16</sup> This type of information generated from correlative studies continues to support the development of new anticancer therapies.

Daugherty et al<sup>19</sup> reported on the perceptions of cancer patients involved in phase I trials, and illustrated that it is the hope for therapeutic benefit that primarily motivates patients, not altruistic feelings. Although patients understand the risks associated with the investigational agents, they often do not have an adequate comprehension of

**Table 5.** Anxiety Levels Reported by Patients and Presumed by MOs and IRBs

Anxiety Level	TPs (%)	CPs (%)	MOs (%)	IRBs (%)
<b>Prebiopsy anxiety</b>				
Normal	70	36	5	3
Borderline abnormal	20	15	85	72
Abnormal	10	31	4	11
Missing data	0	18	6	14
<b>Postbiopsy anxiety</b>				
Normal	90	48	32	24
Borderline abnormal	0	13	60	54
Abnormal	10	19	0	6
Missing data	0	20	8	17
<b>Change in anxiety level</b>				
Less anxiety postbiopsy	20	22	31	27
Same level of anxiety	80	51	61	54
More anxiety postbiopsy	0	6	1	2
Missing data	0	21	7	17
McNemar test, <i>P</i>	.50	< .001	< .001	< .001

Abbreviations: TPs, trial patients; CPs, clinic patients; MOs, medical oncologists; IRBs, institutional review board members.

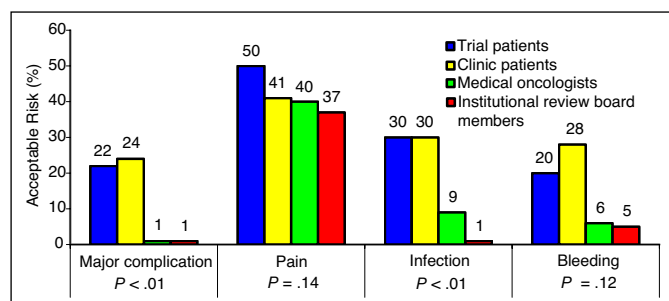
the actual purpose of phase I trials. Our survey supports these data. Although it is stated clearly in our survey that the research-related biopsies are experimental in nature and done solely for research purposes, many patients still believed that having these biopsies might influence their care and health, which clearly indicates patients' persistent hope for therapeutic benefit in these clinical trials. This degree of hope is also reflected in the responses of patients regarding the biopsy-associated risks. When compared with MOs and IRBs, patients are more willing to accept a higher degree of risk. A review of 660 lung biopsy procedures confirms a pneumothorax rate of 23%, but chest tube insertion was needed in only 1%.<sup>20</sup> If done correctly, the risk of a major complication should be less than 2%, which is in keeping with the responses by MOs and IRBs; patients would accept much higher a complication rate to be enrolled into a clinical trial.

HADS was developed to assess the possibility or probability of anxiety disorders and depression among patients in nonpsychiatric hospital clinics.<sup>17</sup> HADS has been used widely and a recent literature review confirms the validity of the scale in assessing symptoms of anxiety disorders and depression in patients and the general popula-

**Table 6.** Perceptions on Additional Testing of the Biopsy Specimens

Question	TPs (%)	CPs (%)	MOs (%)	IRBs (%)
<b>Is it ethical to request the ability to do further testing on tissue if it is of no benefit to the patient?</b>				
Yes			99	86
No			0	10
Missing data			1	4
<b>What should be done with tumor tissue?</b>				
Destroyed	0	4	10	31
Used in research for my type of cancer	10	6	13	13
Used in research for any type of cancer	70	47	74	44
Do not care	20	32	0	0
Missing data	0	12	3	12
<b>Would you allow genetic testing on your biopsy specimen?</b>				
Yes	90	75		
No	0	4		
Uncertain	10	12		
Missing data	0	9		
<b>Should genetic testing on biopsy specimens be requested?</b>				
Yes			82	72
No			4	7
Uncertain			12	15
Missing data			2	7
<b>Would you want to be informed if gene testing revealed information that may affect your health?</b>				
Yes	100	82		
No	0	2		
Uncertain	0	6		
Missing data	0	9		
<b>If genetic testing revealed information that may affect the health of a patient, should they be informed?</b>				
Yes			54	66
No			3	10
Uncertain			28	28
Missing data			7	5

Abbreviations: TPs, trial patients; CPs, clinic patients; MOs, medical oncologists; IRBs, institutional review board members.



**Fig 1.** The percentage of trial patients, clinic patients, medical oncologists, and institutional review board members who would accept a 5% to 10% risk of a major complication, pain, infection, or bleeding associated with the research-related biopsy.

tion.<sup>21</sup> In our study, patients were asked to complete the HADS question items retrospectively based on how they remembered feeling before and after their biopsies. Admittedly, the alternate use of this instrument may influence the validity of our results. The majority of MOs and IRBs perceived that the average patient had a borderline degree of anxiety both before and after the biopsy procedures. As such, they likely have overestimated the degree of anxiety that would be invoked by the mandatory biopsy.

Patients' responses to the survey reflect a willingness to allow their specimens to be used at the discretion of the physicians and scientists involved in the research, once the clinical trial had concluded. Physician responses confirm a desire to procure a tissue bank for additional research needs, whereas 31% of IRBs recommended the destruction of tumor samples, which conflicts with both patients' wishes and MOs' recommendations. IRBs responses may reflect

ethical issues that have been raised by Kodish et al.<sup>22</sup> In their study, IRB chairpersons believed that the quality of current informed consent forms for phase I oncology trials was inferior to consent forms for other types of trials, and were concerned about the vulnerability of the phase I trial participant.<sup>22</sup> These concerns may be the impetus for the IRB responses obtained in our study as well.

Finally, our survey explored attitudes about the disclosure of genetic information obtained through additional research on the biopsy specimens. Our questionnaires specifically asked patients if genetic testing revealed information that may affect their health or the health of their relatives, whether they would want to be informed of the results. We did not ask whether patients would want to be informed of information that would not impact their health, although this would have been an interesting endeavor. Currently, there is no uniform recommendation by a governing body on this issue.<sup>23</sup> The American Society of Clinical Oncology policy statement on genetic testing for cancer susceptibility addresses this issue and recommends a clear dialogue between researchers, IRBs, and patients. Consent forms and authorization for each planned research intention must be obtained before initiation or collection of the specimen. No recommendations are given with respect to the transmission of information once the specimen has been obtained for the purpose of research.<sup>24</sup>

Although interesting observations can be made, there are limitations to our study. Despite being clearly stated otherwise in our survey, about half of the patients still believed that research-related biopsies would have an impact on their health and care. This finding indicates that patients perceive a personal benefit from these biopsies that does

not exist. This perception may thus have an impact on all aspects of the questionnaires, including patients' acceptance of unrelated and genetic testing, as well as their acceptance of risks caused by the biopsies. This perception of personal benefit was not explored in this questionnaire, but additional examination is under evaluation by our group using patient focus groups with an eventual goal of providing a follow-up report on this issue.

These questionnaires are the first to evaluate the perceptions and the impact of undertaking mandatory research-related biopsies in clinical trials. A review of correlative studies in childhood cancer trials stresses that the experimental methods and study design for these trials must be of vital importance to justify the procedure involving more than minimal risk.<sup>4</sup> As long as the research justifies the risk, it is clear that most patients are receptive to having tumor biopsies, tolerate the biopsy procedures, have a minimal degree of associated anxiety, and readily allow their specimens to be tested for research purposes. Patients' understanding of the research nature and lack of personal benefit from these biopsies must be emphasized. Although nearly all MOs see the value of the research-related biopsy, their threshold for acceptable risk is lower than that of patients, and they anticipate more associated anxiety than that reported by patients. IRBs have responses similar to those of the MOs; however, they have a higher threshold for acceptable risk and fewer of them see the value and ethics in requesting the use of the tumor tissues for additional experimentation. Guidelines that represent a consensus view on these issues are needed to ensure safe and ethical conduct in this important area of translational research.

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### ***Appendix***

The Appendix is included in the full-text version of this article, available online at [www.jco.org](http://www.jco.org). It is not included in the PDF version (via Adobe® Reader®).

### ***Authors' Disclosures of Potential Conflicts of Interest***

The authors indicated no potential conflicts of interest.

### ***Author Contributions***

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